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Treatment in Ulcerative Colitis with a Fractional Component of Hog Stomach Extract: In a preliminary report made on the treatment with a dessicated extract of hog stomach ("Ventriculin" Parke, Davis & Company), in idiopathic ulcerative colitis, it was stated that the postulate of an antiproteolytic substance present in the normal bowel precluded the development of ulcerative colitis, and that the deficiency of this substance rendered the patient susceptible to autolysis of the colonic mucosa by proteolytic enzymes. Therefore, the administration of a dessicated extract of hog stomach on the basis that it contained a protective or antiproteolytic substance seemed practical and was supported by the results of clinical improvement and recovery. Stomach extract was used rather than intestinal extract because it was believed that physiologically normal stomach tissue should contain more antiproteolytic substance. Continued clinical investigation and follow-up of the previously reported cases seems further to validate the antiproteolytic concept and its application to therapy.

This report primarily concerns the clinical study of idiopathic ulcerative colitis as it relates to the treatment with a fraction of the dessicated hog stomach after a substantial part of the anti-anemic principle has been removed,to determine whether this fraction contained any of the antiproteolytic substance, and if so, whether it was in greater or lesser concentration than the whole stomach extract. It seemed that if the fraction of hog stomach containing the antiproteolytic substance could be identified, it could be concentrated so that palatability and dosage of higher potency might render the method of treatment even more efficacious, especially in the fulminating type of case. Although this fraction was physically similar to the whole stomach extract, less complaint of unpalatability was experienced by placing one heaping tablespoonful (10 Gm.) of the granules on the tongue and following it by any desired liquid. In this way 3 tablespoonfuls (30 Gm.) were consumed 4 times daily. Occasional complaints of gastric distress were eliminated by the simultaneous administration of dilute hydrochloric acid.

A total of 24 patients were studied for a period of one year. The duration of the disease varied from 6 months to 15 years, and the character of pathology varied from a diffuse inflammatory lesion to that of confluent ulceration and colonic deformity. In this series antibiotic therapy was not resorted to as mentioned in 4 cases in the previous report, even though 3 fulminating cases were encountered. Likewise, of importance is the fact that no dietary restriction was placed on these patients. Their diets were neither low residue nor bland, and there was no vitamin supplementation or supportive therapy. The results of therapy were evaluated primarily by proctosigmoidoscopic examination, and also by radiographic findings. Medication was abruptly stopped when there was no further evidence of an ulceration. Only 4 patients required continuance of therapy after resolution had taken place. Of these 4, one had a history of having had the condition 14 years before therapy; the second had a

history of the disease for 10 years with a resultant deformity and stricture of the large bowel; the third had a markedly fulminating case, complicated by multiple fistulae; and the fourth patient, whose case was mild in character and of one year's duration, required prolonged maintenance dosage because of low tolerance to the fraction (from 10 to 20 Gm. daily). Two of these 4 patients had some degree of relapse after therapy was discontinued for from one to 3 weeks. The remaining 2 patients required readministration of the material when a mild relapse occurred about 3 months after cessation of original therapy. The incidence of relapse was somewhat higher than might result when a routine maintenance dose is used. Apparently a physiological reserve is required in certain cases whereas in others it is not. In those cases having a relapse, it was promptly controlled within from one to 2 weeks, and no further evidence of ulceration appeared. A point worthy of mention regarding the moot consideration of the relapsing-remission character of idiopathic ulcerative colitis is that, in the observation of the author, in a remission not attended by therapy there was evidence on sigmoidoscopy of a degree of mucosal denudation, whereas those patients on therapy with hog stomach extract presented an intact, non-inflammatory mucosa.

It was noted that the more caudal the ulcerating lesions, the higher and more prolonged was the dosage. This is consistent with the concept that the biologic endowment of antiproteolytic substance of the bowel decreases caudally, and therefore repletion of the substance and resultant healing predicates more intensive therapy.

Of those patients with severe gastro-intestinal hypermotility accompanied by from 15 to 20 stools daily, 4 were not favorably affected. It is postulated that in such cases the rapid transit of the hog stomach fraction could not be hydrolyzed and absorbed for maximum utilization. Perhaps when parenteral administration is possible, this factor may be obviated.

Of 3 patients in the chronic and fulminating group that were unfavorably affected, one whose case was fulminating did not tolerate the material and his diarrhea became aggravated. A second patient was partially improved, but continued to lose weight, and because her case was complicated by multiple fistulae and upper respiratory infections, ileostomy was resorted to. The third patient did not follow through on treatment or re-examination and was classified as unimproved. An additional patient with a case of 10 years' duration did respond favorably, but because of multiple polyposis throughout the colon is now being considered for colectomy in view of the question of malignant degeneration.

Constipation was encountered in 6 patients shortly before therapy was interrupted. Because this factor appears to be more predominant than in those patients treated with the whole hog stomach substance, it appears that the hog stomach fraction has a more depressing effect on gastro-intestinal motility than did the whole stomach extract.

As a control, an amount of protein hydrolysate, equivalent to the protein value of the extract of hog stomach, was administered to 8 patients with idiopathic ulcerative colitis who were selected clinically to parallel as closely as possible the group fed the fraction of stomach extract. The duration of administration varied from 6 weeks to 3 months, and averaged 8 weeks. It was found by sigmoidoscopic examination weekly that in all cases but one, bleeding, abdominal cramps and diarrhea persisted. Two patients stated that they felt generally improved, but endoscopic observations revealed the ulcerative process to be static. The above results of protein administration together with the results reported by Machella and Miller seem further to substantiate the fact that when proteolytic enzymes are not in contact with the ulcerated mucosa, resolution will result. The question then arises why those patients with surgical ileostomy do not always recover. In the light of 2 such patients who were treated with fraction of hog stomach, after not responding to surgical interruption of the bowel, and who then subsequently improved, it seems that the antiproteolytic reserve had been exhausted and was inadequate to bring about resolution. In one case an ileitis complicated surgical recovery.

An additional control group of 5 patients who did not have ulcerative colitis but chronic diarrhea of indeterminate origin were administered the fraction of stomach to determine its effect on intestinal motility. It was proved somewhat conclusively in this group that some element of the material did depress motility to a normal state, and if the dosage were not minimized to from 20 to 30 Gm. daily, constipation soon followed. Relapses of intestinal hypermotility were somewhat frequent, but were rather quickly controlled after a few days or a week on therapeutic dosage of the extract. It is assumed that the relapses were predicated upon the fact that the period of therapy was very short, and the very low maintenance dose was inadequate. Whether or not the stomach extract contains any substance such as enterogastrone has not been determined by the author.

From this study, the conclusion is drawn that in treating patients with ulcerative colitis, maintenance therapy beyond the point of recovery is essential in order to maintain colonic integrity. Another interesting observation is that many of these patients were able to tolerate provoking emotional upsets and upper respiratory infections without relapse, which is so prevalent in the untreated patient. This was not always so remarkable in the originally fulminating case. The incidence of constipation in several patients while on therapy, who did not previously experience constipation, is noteworthy, because it appears that some element in the fraction has a depressing effect on intestinal motility. The incidence of gastro-intestinal allergy to pork with resultant aggravation of symptoms in 3 cases is a somewhat disconcerting factor, and of necessity eliminates such patients from this form of therapy. However, 2 of 3 cases were in the mild group and although one young male had a profound diffuse urticaria, he continued with the substance until resolution of the ulcerative colitis had

taken place. The second patient experienced vomiting, gastric distress, and distention, but also persisted until recovery. It is hoped that in the future this can be circumvented by eliminating allergenic properties. Likewise, large dosage and some instances of unpalatability must be considered in dealing with the sensitive patient. In the fulminating case, a more concentrated substance not necessitating such a degree of proteolytic cleavage may counterbalance the loss of hog substance in feces caused by the extreme intestinal hypermotility.

It seems evident that the fractional component of dessicated extract of hog stomach is generally better tolerated and its antiproteolytic property is clinically more potent than the whole substance. However, there have been instances in which a patient was doing well on the ventriculin, and for comparative purposes, was placed on the fraction with resultant aggravation of symptoms and vice versa. Why this phenomenon exists is not understood but this varying selectivity does exist. This study with a hog stomach fraction is perhaps but a phase in the development of an improved antiproteolytic substance, but its present value in the treatment of patients with ulcerative colitis is considered to be worthy of a definite place in the medical armamentarium. The author considers that it further substantiates his concept of the proteolytic pathogenesis of ulcerative colitis. (Am. J. Digest. Dis., Jan. '50, R. Ehrlich)

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Therapy with a Thiosemicarbazone Compound in Tuberculosis: During September 1949, Doctors Hinshaw and McDermott had the privilege of reviewing the results obtained in 10 German institutions during the previous 2 years from the treatment with 4-acetylaminobenzaldehyde thiosemicarbazone in clinical tuberculosis. This drug was originally designated by the code TbI/698, and is now known in Germany by the trade name, conteben. (The proposed proprietary names in the United States are tibione, Schenley Laboratories, Inc., and myrizone, E. R. Squibb and Sons.)

At the time of the review there were reported to be more than 300 hospitals and sanatoriums participating in the clinical trials of conteben and it was estimated that more than 7,000 patients had received treatment with the drug. The institutions chosen for review were among those which had employed the drug since 1947, and which had superior facilities and directors with excellent scientific standing. Also, efforts were made to include visits to physicians and surgeons with various interests in different aspects of the problem under study. In the 10 institutions included in the survey, a total of more than 2,000 patients had received the drug, usually for prolonged periods of time.

Domagk has published evidence that the thiosemicarbazones are effective in vitro and in vivo against Mycobacterium tuberculosis and against tuberculosis produced experimentally in guinea pigs and rabbits. Levaditi has shown that the compound is effective against tuberculosis produced experimentally in mice and concluded that in mice its restraining influence is comparable to that exerted by para-aminosalicylic acid. It is not possible to compare the results in guinea pigs with those which may be obtained with treatment in the experimental disease by promin, promizole, streptomycin, or para-aminosalicylic acid. It is the tentative opinion of one of the authors (H.C.H.) that conteben is less effective than the other drugs named, but this relationship cannot be established until parallel series of studies are completed. Methods of experimentation have been developed which should make an estimation of this comparison possible.

Dosage. Conteben is tolerated by experimental animals much more readily than it is by human beings. Domagk states that mice will tolerate prolonged treatment with as much as 5.0 Gm. per Kg. per day orally. In contrast, human beings will tolerate only about 0.005 Gm. per Kg. per day (equivalent to 0.35 Gm. for a person weighing 70 Kg.). In other words, mice and guinea pigs tolerate from 100 to 1,000 times as much of the drug, if computation is made on a body weight basis. The potential fallacies of such figures are well recognized, but because methods have only recently been developed for determination of thiosemicarbazone concentrations in body fluids, no other basis for comparison is available. The clinicians visited were not in complete agreement regarding what constituted the optimal daily dose. The recommendations ranged from a low of 0.0125 to 0.025 Gm. of conteben per day to 0.1 to 0.3 Gm. per day. In general, an initial dose of 0.05 Gm. per day for one or 2 weeks with gradual increase to 0.2 Gm. per day was recommended. A maintenance of constant blood levels was not considered to be essential and oral doses were given from one to 4 times daily. All clinicians agreed that very prolonged treatment was desirable, the average recommendation being perhaps 6 months, although some patients have been treated continuously for more than a year.

Gastro-intestinal manifestations of toxicity. Anorexia, malaise, and occasional vomiting appeared to be the principal factors limiting dosage. These symptoms subsided when the dose was reduced or treatment temporarily interrupted. It was estimated by Heymer that about 10 percent of patients will suffer gastro-intestinal disturbances on a total daily dose of from 2 to 4 mg. per Kg. body weight. Boehm and Brecke observed anorexia in 44 percent of patients, and it was severe enough to require discontinuation of treatment in 8.6 percent of patients. Their recommendations for dosage ranged from 0.05 to 0.2 Gm. per patient per day.

Vomiting was observed occasionally by other observers when larger doses were employed and Boehm and Brecke report vomiting in 17 percent of their series of 245 patients.

Jaundice and fatty infiltration of the liver. Because of uncertainty concerning toxicity to the liver, a special meeting was held in July 1949 at Moln for the purpose of considering this problem. All of the approximately 20 attending investigators reported that jaundice was a common condition among both treated and untreated patients, but usually occurred more frequently among those treated. It was postulated that this might be, at least in part, homologous serum jaundice transmitted by needles and syringes, for studies involving venipuncture were frequently carried out on patients under thiosemicarbazone treatment. The problem of the relation of conteben to hepatitis must remain an open question, but, based upon the appearance of the liver by laparotomy, peritoneoscopy, and at autopsy, it seems reasonable to assume, until evidence to the contrary is available, that the drug is capable of inducing hepatitis.

Agranulocytosis. Eight instances of agranulocytosis among 2,000 patients who received conteben were reported to the authors. In both of Heilmeyer's cases and in several of the others, the patients had been receiving aminopyrine at the time of the appearance of agranulocytosis. Assuming that the over-all incidence of agranulocytosis is of this order (approximately 4 per 1,000), the use of the drug would not be invalidated but careful observation of leukocyte counts would be a necessary precaution during treatment.

Effects upon hematopoietic system, serum proteins, and erythrocyte sedimentation rate. Heilmeyer had observed one hemolytic crisis which he attributed to conteben therapy. Pribilla and Loester of Essen reported 6 hemolytic reactions. Most of these patients received 0.5 Gm. daily, a dose now considered to be well within the toxic range. With the doses now in use (from 0.050 to 0.2 Gm. daily), hemolytic crises have not been observed elsewhere and must be considered to be a relatively rare complication. An unknown percentage of patients (apparently less than one half) developed anemia of mild degree after receiving conteben treatment. Except for the hemolytic crises mentioned above, the lowest concentration of hemoglobin noted during drug-induced anemia was 60 percent. Kuhlmann has utilized transfusions quite frequently but more to restore depleted serum proteins than for treatment of anemia. He stated that patients with initial anemia and hypoproteinemia do not respond to thiosemicarbazone therapy. He believes that serum albumin transports the drug in the blood stream, but did not give the evidence for this hypothesis. There was great interest in the subject of serum proteins in tuberculosis and several centers are carrying out electrophoresis studies. They note an increase in gamma globulins as the patient's condition improves during conteben therapy and as this fraction includes certain antibodies they regard the finding as a favorable one. A strange and potentially deceiving effect of conteben therapy has been observed repeatedly in determinations of the sedimentation rate of erythrocytes. Within a few days of the start of treatment there is usually an impressive decrease in sedimentation rate with

high values returning to essentially normal levels. Heilmeyer has made a special study of this phenomenon and has concluded that it is a nonspecific effect occurring in patients with and without tuberculosis. He believes, therefore, that the sedimentation rate loses its import as an index of improvement during conteben therapy. Nevertheless, other investigators often stressed the decreased erythrocyte sedimentation rate as evidence of therapeutic effect.

Central nervous system toxicity. Investigators using the standard dosage have not recognized any significant central nervous system symptoms or findings except for the rather high incidence of headache and dizziness reported by Boehm and Brecke.

Renal toxicity. Malluche reported mild albuminuria occasionally but neither he nor any other investigator regarded conteben as a nephrotoxic drug. Heymer has treated 7 patients who had amyloidosis with renal damage, and they tolerated the drug satisfactorily.

Several investigators were questioned concerning the possibility of nitrogen retention or other evidence of impairment of renal function, and a negative answer was always obtained. Martini had observed renal function with special care in patients receiving conteben and concluded that renal damage was no hazard.

Skin rashes and conjunctivities. Exanthems were observed by all investigators. Usually the eruption consisted of a toxic erythema or morbilliform rash, but occasionally urticarial or rarely petechial eruptions were described. Pribilla and Koester have reported the occurrence of one fatality during an allergic reaction to conteben. The course of events in this case was similar to that observed during toxic reactions to sulfonamides. Conjunctivitis was also seen by nearly every observer, but only occasionally, and never did the reaction reach alarming proportions. It should be mentioned here that the earlier preparations of conteben were combined with sulfathiazole and from the records it was not always possible to exclude the participation of sulfathiazole in toxic reactions. No instances of exfoliative dermatitis were reported to the writer of this report.

Therapeutic effectiveness. The problem of the evaluation of any drug in the treatment of tuberculosis is difficult, but is particularly so when it is universally agreed that the drug is not sufficiently powerful to exert an impressive effect upon the course of miliary or meningeal tuberculosis. This is the case with conteben, and the problem is further complicated by the fact that a radical improvement in the nutritional status of the patients (notably the repatriated war prisoners) coincided with the period of drug-testing. Moreover, the supply of roentgenographic film in Western Germany has not been abundant and many of the patients in the conteben study had to be examined by the use of

paper film. Nevertheless, despite these handicaps, it was possible to arrive at certain conclusions on the basis of the evidence presented to the reviewers.

Tuberculous meningitis and miliary tuberculosis. Except possibly for one case, little or no effect was reported for conteben medication in tuberculous meningitis, and streptomycin was regarded as the choice for therapy. The clinicians are not willing to withhold streptomycin from such patients when it can be obtained. Kuhlmann treated 3 patients with tuberculous meningitis with conteben when he was unable to obtain streptomycin, and all 3 died. He thought that their lives may have been prolonged for a few weeks. The situation with miliary tuberculosis was similar and the authors saw no instance of classical generalized hematogenous miliary tuberculosis with recovery unless streptomycin had been administered. It is now the general practice in Germany to administer streptomycin immediately to all patients with meningeal or miliary tuberculosis.

Laryngeal tuberculosis. The effect of conteben therapy in tuberculosis of the larynx was uniformly impressive and resembled the effects of streptomycin. The pain and dysphagia of severe, ulcerative, tuberculous laryngitis was reported to disappear within a few days; hoarseness disappeared, and subsequently the lesions improved objectively over a period of several weeks. Complete healing of the lesions has been observed almost uniformly within a period of from 6 to 8 weeks. The authors talked with patients who described their dramatic improvement and these patients spoke with nearly normal voices The number of patients with tuberculosis of the larynx treated by the various observers must total nearly 200 and the favorable results were variously estimated at from 90 to 100 percent good to excellent. New lesions have appeared during treatment, however, but rarely after the first few weeks. The results in these laryngeal cases constitute acceptable evidence that conteben has a definite effect on tuberculosis.

Tuberculous enteritis. Tuberculous enteritis appeared to be unusually common among patients in German sanatoriums. Virtually all of the investigators placed a great emphasis on roentgenographic findings in both the diagnosis and the continued observation of patients with this form of tuberculosis. As a consequence, in the majority (possibly as many as two thirds) of the patients who received conteben for alleged intestinal tuberculosis, the diagnosis was based entirely on roentgenographic findings. For example, in Boehm's series of 42 cases of tuberculous enteritis, two thirds were asymptomatic. Kuhlmann was also particularly interested in intestinal tuberculosis and estimated that he had treated from 60 to 70 patients. Heymer has treated from 30 to 40 patients and each of the other investigators has treated at least a few patients with intestinal tuberculosis, and often a considerable number. In these series also, the diagnosis was made solely by roentgenographic study in a large number of the cases. This point is emphasized because the reviewers believe that

roentgenographic studies of the intestine are an unreliable index by which to evaluate the effectiveness of an antituberculous drug.

Every investigator was questioned directly and each responded that 100 percent of all patients with symptoms of intestinal tuberculosis obtained relief with conteben therapy. Diarrhea ceases within a few days usually and pain is quickly eased. Fever subsides within a few weeks at most and eventually roentgenologic evidence of healing is observed. Many clinical records demonstrating these findings were shown to the reviewers. As tuberculous enteritis is such a grave complication of pulmonary tuberculosis and is usually refractory to all treatment except chemotherapy, the authors could not but accept this as evidence that conteben has a clinically recognizable antituberculous activity. It is interesting to note that conteben, like streptomycin and para-aminosalicylic acid, is peculiarly effective against tuberculous enteritis.

Brecke and Boehm described 4 patients whose tuberculous enteritis healed with cicatricial deformities producing intestinal obstruction and requiring resection. The resected bowel was examined microscopically and ulcerations were healed, but there were remnants of tuberculous infiltration in the submucosal zones. Malluche reported similar findings in one or more cases.

Exacerbations of symptoms of tuberculous enteritis have been observed after cessation of therapy and these have again responded to conteben therapy. Prolonged treatment (perhaps 6 months) appears to be desirable in cases of tuberculous enteritis.

Pulmonary tuberculosis. It was obvious that the German investigators were plagued with the same difficulties in evaluating conteben in pulmonary tuberculosis as had been faced by those who sought to evaluate sulfone drugs and streptomycin. Evaluation is made more difficult by the fact that treatment was undertaken in the past 2 years during which time nutrition and medical care has improved in Germany to an impressive degree. Furthermore, this has been a period when considerable numbers of prisoners of war have been returning, especially from eastern Europe, often in deplorable physical condition, and have been receiving simultaneously and for the first time, good food, rest, good nursing care, and good medical supervision, as well as conteben. The German physicians recognize this factor in most instances, but expressed the unqualified opinion that conteben had played a significant part in the remarkable recovery of some of these patients. The reviewers were shown a large number of cases in which an impressive degree of roentgenographic clearing of pulmonary lesions had occurred during relatively prolonged conteben therapy (from 4 to 6 or 9 months). There was no question concerning the fact that the patients had attained excellent results, but it was not possible to relate the results with absolute certainty to the administration of conteben.

The reviewers repeatedly were shown films of patients which demonstrated reduction in size of cavities, leading them to suspect a favorable effect of the drug upon endobronchial tuberculosis, although bronchoscopy was rarely performed. Furthermore, the tomographic films demonstrated were not always comparable, as depth measurements were obviously inaccurate in at least a few instances. Malluche was exceedingly enthusiastic about combining local intracavitary treatment (conteben suspended in glycerin) with the Monaldi drainage maneuver. Without such cavernostomy, he has seen little or no favorable effect of the drug on giant cavities. He has applied such combined treatment in 48 cases, mostly during 1949, and unquestionably the early results are superior to any treatment for patients with giant cavities previously observed by the authors. Whether these cavities will reopen remains to be seen; certainly this has occurred frequently when the Monaldi procedure is used alone. He reported that the cavernostomy fistulas uniformly close within a few days after removal of the tube, thus obviating one of the most serious handicaps to the Monaldi procedure. He obtained proof of cavity closure by roentgenographic examinations after instillation of iodized oil before removing the drainage tube.

German physicians whom the authors interviewed agreed that conteben treatment, like streptomycin treatment, is but one phase of medical treatment in tuberculosis. They often expressed the belief that conteben could be used more frequently than streptomycin, and it appeared that they were using it almost routinely in some institutions. Conteben, like streptomycin, has apparently permitted physicians to be more radical in their employment of collapse procedures, especially pneumothorax. Pulmonary resection for tuberculosis is not widely used in Germany; hence, it remains to be seen if conteben offers adequate protection against the tuberculous complications of lobectomy and pneumonectomy.

The general consensus of physicians interviewed was that conteben, like streptomycin, is most likely to affect favorably fresh-exudative, nondestructive types of pulmonary tuberculosis. It is also a general opinion that conteben is neither as dependable nor as rapid in its action on pulmonary lesions as is streptomycin. Several expressed the opinion that conteben should dirst be tried and, if unsuccessful, streptomycin or para-aminosalicylic acid should be added. The economic factor also entered into this reasoning, for both streptomycin and para-aminosalicylic acid require dollar exchange and are expensive, whereas conteben is said to be a much cheaper drug in addition to its being a local product in Germany.

Only a little evidence was produced to indicate that thiosemicarbazone-resistant organisms may eventually appear in clinical infections (5 cases of Brecke and Boehm), and no bacteriologic studies of sensitivity were made.

No studies have been made to determine if conteben administered with streptomycin will delay the emergence of streptomycin-resistant bacilli. On theoretical grounds the authors believe that such might prove to be the case. If such a study showed no such effect, however, it would tend to shake the reviewers' faith in the value of conteben in pulmonary tuberculosis.

Tuberculous empyema. Conteben has developed a good reputation in Germany as a remedy for tuberculous empyema when introduced as aqueous suspension directly into the infected pleural space. Most of the cases presented were instances of empyema developing after closed intrapleural pneumonolysis by cautery, and treatment consisted not only of local conteben therapy, but also pleural lavage, azochloramide, and oral conteben treatment. When bronchopleural fistulas were present (cavity "blow out") the results were very poor, as is true with all other therapeutic approaches to this situation.

Specific recommendations made by Malluche were that from 0.1 to 0.3 Gm. of conteben in an aqueous suspension (from 10 to 20 percent) be instilled every few days into the infected pleural space by needle puncture. Kuhlman also presented several cases, utilizing similar methods and also employing Tb. VI intrapleurally in some cases. (Domagk told the authors that TbI (conteben) and Tb. VI are essentially the same drug except that the former is very insoluble in water and the latter is soluble, making it more suitable for local and parenteral use.)

Because streptomycin has proved to be of so little value in the treatment of tuberculous empyema, this may be an important use for conteben treatment if these results can be confirmed.

Genitourinary tract tuberculosis. Boshamer has treated about 50 patients with genitourinary tract tuberculosis with reported excellent results. Bladder ulcerations and the resultant symptoms improved rapidly; bacilli in the urine were reduced in number, but were rarely eradicated, and renal lesions improved but little pyelographically. Kuhlmann described 4 patients with renal tuberculosis treated with good results and he said that he had treated 4 or 5 patients with tuberculous epididymitis with excellent results. One of these patients was demonstrated to the authors, but open draining sinuses were still present and the result would not compare favorably with that which the authors are accustomed to see following streptomycin therapy. Domagk demonstrated a prostate obtained at autopsy which showed what he believed to be remarkable healing of tuberculous prostatitis.

It should be emphasized that because of the nature of this type of tuberculosis and the relatively few patients treated by each investigator, the statements made concerning conteben in genitourinary tuberculosis have really no more weight as evidence than hearsay. The treatment in genito-urinary tract

tuberculosis requires that the antibacterial action of the drug be long continued, and the authors believe that duration of action may be more important than intensity of action. Hence conteben might prove to be especially adaptable for treatment in this condition.

Tuberculous sinuses, fistulas, and abscesses. Several observers have treated small series of patients with draining sinuses and fistulas with or without localized abscess formation. Although all agreed that the drug has a favorable effect, none were able to obtain results which compare favorably with those obtained in the United States with streptomycin therapy. Results were slower in appearing, less convincing, and perhaps less permanent than with streptomycin.

Malluche had instilled aqueous suspensions of conteben directly into cold abscesses, especially those associated with bone tuberculosis, with results which he regarded as excellent. He presented films and detailed charts of 2 such patients to the authors. The tissues apparently tolerate the drug quite well, and perhaps the insolubility of the drug is a desirable attribute because a depot of the antibacterial agent is presumably established at the site of the disease process.

Hinshaw and McDermott conclude that the data which have been assembled on the use of conteben in tuberculosis in Germany fully justify a prompt and thorough series of experimental and clinical trials in the United States. (Am. Rev. Tuberc., Jan. '50, H. C. Hinshaw and W. McDermott)

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The Status of Conteben in Tuberculosis: A review has been made of the collected experiences with conteben (TbI/698), a substance of the thiosemicarbazone series which has been used in Germany in the treatment of over 10,000 patients with various forms of tuberculosis.

Miliary tuberculosis and tuberculous meningitis are not satisfactorily controlled by conteben therapy.

In pulmonary tuberculosis the activity of conteben is shown most clearly if the lesion is associated with a perifocal inflammatory process. The more labile the lesions and the better the blood supply therein appears to be, the more promising is the thiosemicarbazone therapy. Chronic stabilized cases of pulmonary tuberculosis react, as would be expected, less satisfactorily to thiosemicarbazone medication.

Cavernous processes often respond very impressively to oral administration of the drug. Intracavernous thiosemicarbazone treatment promises

success even in severe, progressive, cavernous processes. Conteben has apparently proved satisfactory in the preparation of patients for operation and for controlling postoperative complications.

The best tendency toward healing has been shown in mucous membrane lesions, such as tuberculous of the bronchi, trachea, larynx, intestine, and urinary bladder.

The experiences with thiosemicarbazone therapy do not yet permit a final judgment of its effectiveness in renal tuberculosis, but certain of the preliminary reports are encouraging. Similarly, no final judgment is possible on the degree of response in bone and joint tuberculosis to thiosemicarbazone therapy. Tuberculosis of the soft parts, particularly with the formation of fistulas, however, may already be included among the fields in which the preparation is definitely indicated.

In thiosemicarbazone therapy the dosage must be adapted to the form and the stage of the tuberculous process, the responsiveness of the manifestation of tuberculosis, and the respective individual tolerance of the patient. The usual daily dose of conteben for adults amounts to approximately 0.002 Gm. per Kg. administered by the oral route.

Thiosemicarbazone therapy is not free from toxic effects. At the beginning of the clinical tests, toxic phenomena were extensively produced because of ignorance of the most suitable dosage and the peculiarities of the mode of action of the drug. Many of these reactions are completely avoidable today within the range of the guidelines for dosage which have been tested and proved satisfactory. At the beginning of therapy, lack of appetite and gastric complaints are not rare. These phenomena usually disappear in spite of continuation of the administration of the drug. Exanthems, which are frequently preceded by conjunctivitis, have been observed.

Within the range of the dosage now recommended, anemias are relatively rare, but in larger doses (0.3 Gm. per day or more) they are more frequent and are hemolytic in type.

Agranulocytosis and granulocytopenia during the course of therapy have been observed. Consequently, it is essential that all patients on thiosemicarbazone therapy be carefully observed for the possible occurrence of this reaction.

The effect of conteben therapy upon the liver function has not yet been determined unequivocally. Under thiosemicarbazone therapy the more or less strongly marked tendency in tuberculosis toward the development of a fatty liver may occur to an increased degree. This process is apparently reversible

and, in a few instances, could no longer be detected laparoscopically from 10 to 12 weeks after discontinuing the medication. (Am. Rev. Tuberc., Jan. '50, A. Mertens and R. Bunge of the Laboratories of the Farbenfabriken Bayer at the Elberfeld Works, Leverkusen, Germany)

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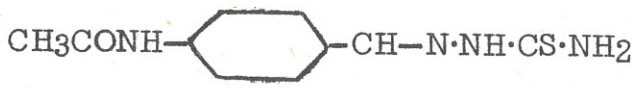
Properties of Conteben: Of the multiplicity of substances recommended for treatment in tuberculosis, compounds from 3 different classes of substances have at present won particular importance: the glucoside streptomycin, belonging to the series of antibiotics; para-aminosalicylic acid; and the thiosemicarbazones, particularly 4-acetylaminobenzaldehyde thiosemicarbazone (conteben, or TbI/698), with the structural formula,



Conteben is a pale yellow, finely crystalline powder of bitter taste. It has the formula $C_{10}H_{12}ON_4S$, a molecular weight of 236.28, and melts with decomposition at about 230° C. This compound is almost insoluble in water. In 100 cc. of water 0.0088 Gm. dissolves at 20° C., and 0.0172 Gm. at 37° C. The solubility is very dependent upon the pH. Human urine is able to retain a multiple of these quantities in solution. Clinical investigations have indicated that the solubility of the compound in serum is better than in water alone. Conteben is only sparingly soluble in alcohol, acetone, and chloroform, but on warming is soluble in dilute aqueous caustic soda, glycerol, and acetic acid; at room temperature it is even soluble in ethanolic and methanolic caustic soda.

In 2 cc. of 50 percent sulfuric acid, 0.2 Gm. of conteben dissolves without warming to a clear light yellow liquid. If 0.1 Gm. of sodium nitrite is added to the solution, the latter then becomes intensely red in color. If 0.1 Gm. of conteben is dissolved in 5 cc. of dilute caustic soda, and 2 cc. of lead acetate solution are added and the mixture is boiled, the solution becomes dark in color with the separation of black flecks of lead sulfide. The addition of copper sulfate solution to a solution of conteben in 50 percent sulfuric acid precipitates the gray-green copper complex salt. This reaction is extraordinarily sensitive and also indicates small amounts of conteben by a green coloration. Conteben has proved to be an excellent producer of complex compounds and also yields insoluble complex salts with other heavy metals.

In spite of its slight solubility in water, the use of conteben is not confined to administration by mouth. By means of the addition of solubilizing agents like antipyrine, it becomes possible to increase the solubility of conteben so that the preparation may be used for injection therapy. Suitable solutions for injection also can be prepared in glycols, like 1-2 propylene glycol, or acid amides, like formamide and methylacetamide.

In case highly concentrated neutral aqueous solutions of a thiosemicarbazone are required for special therapeutic purposes, then, in place of conteben, other compounds of the thiosemicarbazone series must be adapted, the suitability of which for the desired special purpose is still the subject of detailed investigation. (Am. Rev. Tuberc., Jan. '50, R. Behnisch et al. of the Laboratories of the Farbenfabriken Bayer at the Elberfeld Works, Leverkusen, Germany)

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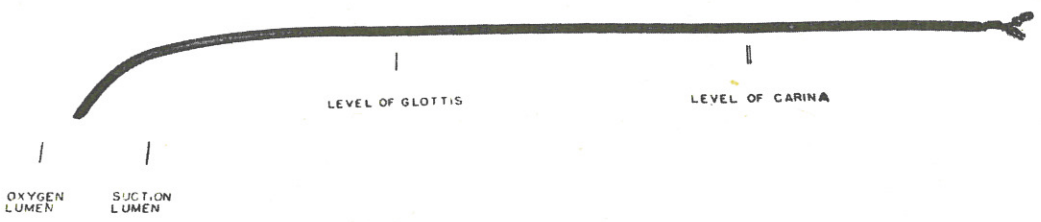
A Double Lumen Intratracheal Tube for Simultaneous Oxygen Administration and Tracheobronchial Aspiration: Many patients with heart and lung diseases examined at necropsy are found to have collections of thick, mucoid secretions in the tracheobronchial tree which could be considered as the immediate cause of death. In order to prevent collection of these thick mucoid secretions which the patient is unable to expel and to insure adequate oxygen, a new type of tube (made by George P. Pilling & Son Co., Phila., Pa.) has been developed which is inserted in the trachea or main stem bronchus and allowed to remain for long periods of time. The double lumen of the tube permits simultaneous oxygen administration and either continuous or intermittent aspiration of the tracheobronchial tree. This eliminates the possibility of withdrawing alveolar gases that might occur with suction through a small single tube with the vocal cords closed around it. The tube is useful in the postoperative patient and particularly in any comatose or semicomatose patient who is unable to expel tracheobronchial secretions and who is in need of oxygen. In patients in whom pulmonary transudates have accumulated following trauma, accidental or operative, with development of the so-called wet lung, the dyspnea may be relieved and fluid removed by use of the indwelling double lumen tube. Chest and neurosurgical patients who normally must be sedated with great care to avoid dulling the cough reflex, can safely receive more narcotics when the tracheobronchial secretions are aspirated.

The tube, shown below, is 20 French caliber. The suction lumen is 5 mm. wide and the oxygen lumen is 3 mm. wide. The distal 10 cm. has a molded curve which is modeled after the Magill endotracheal tube. This facilitates introduction of the tube through the glottis, and aids in exact placement in either main stem bronchus. There is a longitudinal line extending from the tip on the



concave side of the curve which aids in placing the tube in the trachea through the glottis but is invaluable in orientation of the tip when introducing it in either main stem bronchus. There are 2 transverse markers. The first one, 18 cm. from the beveled tip, indicates the approximate distance of the glottis from the nares. The second marker, 32 cm. from the beveled tip, represents the approximate distance of the carina from the nares. Prior to manufacture of this specially designed tube, a portion of a Miller-Abbott double lumen intestinal tube was used for simultaneous aspiration and oxygen administration. However, the small lumen frequently precluded aspiration of the thick, viscous secretions.

Oxygen is administered from a tank or a pipe line with a suitable regulator, flow meter, and humidifier. The author feels that it is important to have the oxygen humidified. Any suction device may be employed to withdraw the secretion from the tracheobronchial tree.

Intratracheal suction, which was continuous, was first used quite accidentally, upon a postoperative chest patient at the Pennsylvania Hospital, Philadelphia, in 1945. Following resection of a carcinoma of the esophagus, a Levine tube was supposedly introduced in the esophagus and suction applied as well as intranasal oxygen. A routine chest film 24 hours later demonstrated that the tube was in the trachea. On removal, the patient developed obvious collections of tracheobronchial secretions which previously had been aspirated. In retrospect it was felt that the continuous suction of the trachea had been beneficial in maintaining a clear airway, and no ill effect was observed during its use with nasal oxygen.

The technic of passage of an intratracheal tube is familiar to the anesthetist and bronchoscopist, but the average intern or resident has little training or experience in passing endotracheal tubes, and considers blind passage a formidable procedure. Actually, by using a few simple precautions, blind passage can be accomplished even in the comatose patient. Cocaine or pontocain is used to anesthetize and shrink the mucous membrane of the nasal mucosa and nasopharynx. The tube, which is lubricated with nupercaine ointment, is then inserted gently and smoothly through the inferior meatus. As the pharynx is approached, the head is tilted backward or extended. It is this positioning that, in the author's experience is important in passage of the tube into the trachea, although Magill recommended that the mandible should be held at right angles to the cervical spine. The maneuver seems to open the glottis and the esophagus cannot be entered with ease. In contrast, the head, when sharply flexed, will usually result in the tube entering the esophagus because the epiglottis covers the tracheal opening. Thus, by carefully positioning the head, a tube can be introduced at will in either the esophagus or trachea. Some manipulation of the tube is frequently necessary if the tube is too far laterally and impinging against the pyriform fossa, or if it is too far anteriorly and resting

upon the anterior commissure. The longitudinal line indicates the concavity of the curve at the distal end which aids in guiding the beveled tip into the trachea through the vocal cords.

Ideally, the end of the tube when in place should lie between the cricoid cartilage and the bifurcation of the trachea. The proper length to be inserted can be measured by laying the tube alongside the patient's neck. The trachea bifurcates at the angle of Louis and the beveled end measured from the nares to this point will determine the point of the carina in relation to the tube markers. Because the level of the carina can be established in relation to the markers on the tube, the carina can be stimulated and produce a definite activation of the cough reflex, even in the comatose patient. Secretions are thus removed from the bronchioles despite the fact that the distal end does not reach these finer air passages. If aspiration of one or the other of the main stem bronchi is desired, the curve is directed toward this lung by rotating the tube using the longitudinal line as an indicator of the direction of the concavity at the distal end. The right main stem bronchus usually can be entered with ease, but because of the more acuteness of the angle more precise manipulation must be done to enter the left bronchus.

At times the suction lumen may become clogged with thick, viscid secretions. It may not be necessary to withdraw the tube in order to dislodge the plug because temporarily changing the oxygen flow to the suction side will open the lumen. However, in cases in which the tube is allowed to remain endotracheally for long periods of time, it is recommended that routine removal and cleaning be performed once or twice every 24 hours.

Experience has shown that usually 6 liters of oxygen per minute are sufficient to maintain adequate oxygenation. However, only by direct experiment can the amount of oxygen needed be determined. The most reliable physical signs are pulse and color, and repeated observations will indicate whether flow is adequate.

It would seem that the use of an indwelling tube for long periods of time would have certain hazards. However, the trachea and vocal cords have been inspected at postmortem examination of patients in whom the tube has been in place for as long as 6 days, and no ulceration or even unusual hyperemia have been demonstrated. Lundy felt that any complication that develops following prolonged intubation results more from the trauma of introduction rather than from the presence of the tube lying in the trachea. He warned, however, of the potential danger of introducing organisms foreign to the patients by careless cleansing and intubation. Gillespie cited 2 important considerations which should be observed when an endotracheal tube remains in place: (1) liquids must be administered carefully for they may be easily aspirated because the

cords do not close tightly; (2) the tube should be changed every 12 hours and cleaned because of dried mucous collections. The double lumen of the tube prevents positive intrabronchial pressure developing from oxygen administration. Precautions must be taken to prevent fire and explosion when high concentrations of oxygen are used with open electric suction machines. (Surgery, Jan. '50, R. A. Buyers)

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Terramycin: A. C. Finlay et al. of the research laboratories of Chas. Pfizer & Co., Inc, have isolated a new crystalline antibiotic, Terramycin, from cultures of a new actinomycete, Streptomyces rimosus.

Terramycin is amphoteric and forms the crystalline hydrochloride and sodium salt. Crystalline terramycin is soluble in methanol, ethanol, acetone, and propylene glycol, in water to the extent of 0.25 mg. per ml. at 25° C; insoluble in ether and petroleum ether. Terramycin is stable over long periods in aqueous solutions of about pH 2.0-5.0 at room temperature.

The activity in vitro of crystalline terramycin hydrochloride against a variety of micro-organisms is shown below.

Species	µg./ml.	Percent Inhibition
Aerobacter aerogenes	1.0	100
Klebsiella pneumoniae	3.0	"
Escherichia coli	5.0	"
Salmonella typhosa	3.0	"
Salmonella paratyphi	1.0	"
Salmonella schottmuelleri	1.0	"
Salmonella pullorum	10.0	"
Shigella paradysenteriae	1.0	"
Bacillus subtilis (FDA219)	3.0	"
Staphylococcus albus	1.0	"
Staphylococcus aureus	1.0	"
Proteus sp.	> 1000.0	"
Pseudomonas aeruginosa	100.0	"
Brucella bronchisepticae	3.0	"

Activity is expressed in terms of the equivalent weight (µg.) of crystalline terramycin necessary to inhibit growth.

Terramycin shows a low degree of toxicity in animals. The intravenous LD_0 for terramycin hydrochloride is equivalent to 103 mg. of the crystalline amphoteric compound per Kg. of body weight in mice; the LD_{50} is equivalent to 192 mg. per Kg.

As in the case with aureomycin and chloramphenicol, terramycin is active in vivo as well as in vitro and displays marked chemotherapeutic activity against experimental infections in mice produced by Streptococcus hemolyticus, Diplococcus pneumoniae, Klebsiella pneumoniae, Salmonella typhosa, and other organisms. It is effective by both the oral and parenteral routes of administration. Preliminary studies suggest that terramycin has definite antirickettsial activity in the chick embryo. In high concentrations it appears to inhibit the infection of the chick embryo with the PR8 strain of Influenza A virus. (Science, 27 Jan. '50)

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Effects of Carbon Dioxide Oxygen Mixtures Given During Preheadache Phase of the Migraine Attack: A large body of clinical and experimental studies have illuminated some of the changes which take place during an attack of migraine. The pain of this headache is known to arise from dilated arteries either inside or outside of the head, or both. Certain of the preheadache phenomena have been studied and have been shown to be the result of cerebral vasoconstriction.

In an attempt to study the vasoconstrictor phase further, a number of patients were given carbon dioxide by inhalation in the laboratory. Carbon dioxide was used in these studies primarily because it is known to exert a potent vasodilator influence on cerebral arteries. In their reactions to carbon dioxide, the cerebral vessels were sensitive, as well as prompt, and the magnitude of their response is great. All sizes of vessels in all parts of the brain respond to the drug. Second, carbon dioxide does not produce headaches, as does histamine administered intravenously. Third, carbon dioxide is a physiologic agent and appears to play an integral part in the normal vasoregulatory mechanism of the head. A fourth consideration in its selection is the important fact that it is simple to administer and is easy for the patient to accept.

Carbon dioxide in 10-percent concentration was administered by face mask to recumbent patients for 3 periods of 5 minutes each. From 5 to 15 minutes was allowed between trials to permit observation of the effect of the procedure and to allow the patient to rest after the exertion of the profound hyperventilation produced. The same technic was used in each experiment. If no effect was obtained after 3 trials the procedure was discontinued. Mixtures of 10-percent carbon dioxide in air and of 10-percent carbon dioxide with 90-percent oxygen were used in these experiments. The mixture used was not known to the patient. The pulse and blood pressure remained within the range of normal throughout all trials.

The carbon dioxide mixtures were administered during one of the 3 phases of the migraine attack: during the vasoconstriction stage, before the headache,

during the interval when vasoconstrictor phenomena overlapped the painful vasodilator phase, and when the headache alone was present.

A total of 25 trials were carried out on 15 patients. In 5 instances only vasoconstrictor phenomena were present. In these, carbon dioxide-air mixtures produced transient clearing of the visual distrubances with return of symptoms to their former intensity within 5 minutes after inhalation of the gas was discontinued. When the carbon dioxide-air combination was followed by the carbon dioxide-oxygen mixture in similar amounts or when the carbon dioxide-oxygen mixture was used alone, vision cleared promptly and remained so. The expected headache did not follow.

One subject experienced extreme sleepiness and nausea as preheadache manifestations. Ordinarily these disappeared as the headache developed. During inhalation of the carbon dioxide-oxygen mixture, the patient became alert; her nausea disappeared in less than the usual interval and the expected headache did not follow. When headache was present, the results were so unpredictable that no conclusion could be drawn. The headache was not increased by the procedure except in one subject.

From these experiments, 2 inferences may be drawn: first, carbon dioxide, a powerful physiologic intracranial vasodilator, is effective in decreasing or abolishing the intracranial vasoconstrictor phenomenon of the migraine attack. Second, oxygen when used in combination with carbon dioxide makes these effects more pronounced and may prevent the progression of the attack.

The effect of carbon dioxide-oxygen mixtures observed here is similar to but more pronounced than the effect of oxygen when used alone, as reported by others. Furthermore the effects on the peripheral phenomena are more predictable. In Alvarez' series, complete relief was noted in 42 percent of the patients with apparently typical migraine, and 44 percent were helped. He found that 100-percent oxygen had to be inhaled for periods ranging from 15 to 120 minutes to produce these results.

The superiority of the combination of carbon dioxide and oxygen may rest on a dual effect. Inhalation of carbon dioxide in 10 percent concentration alone was found to double the cerebral blood flow in one series. Kety and Schmidt reported that 5.7-percent carbon dioxide produced a 75 percent increase in blood flow as measured by the nitrous oxide technic. It is therefore postulated that the greatly increased amount of blood which is maximally saturated with oxygen corrects an underlying oxygen deficiency in a strategic area of the brain, where the neural impulses which set up the compensatory vascular dilatation of the migraine attack may originate. This postulation fits

into the broader concept that the painful stage of vasodilatation is an attempt on the part of the organism to restore cranial circulatory stability.

Although these studies have not shown that the use of carbon dioxide-oxygen mixtures is entirely predictable, they indicate that the migraine attacks can be interrupted before the headache develops. Further, they suggest that vasoconstriction is a constant feature of the type of attack studied and may persist into the period of painful vasodilatation.

A variety of vasodilators have been advocated in the therapy of migraine. Results have been varied and unpredictable, but in general it has been found that these substances are more likely to eliminate headache if used at the very onset of pain. That they have sometimes achieved this effect suggests that they operate in a manner similar to that proposed for carbon dioxide in these studies. (Arch. Neurol. and Psychiat., Jan. '50, R. M. Marcussen and H. G. Wolff)

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Desoxycorticosterone Acetate and Ascorbic Acid in Rheumatoid Arthritis: In a letter to the editor of the Lancet, the writer, working in the Rodogoszcz Municipal Hospital, Lodz, Poland, states that he applied the method described by Lewin and Wassen in 9 cases of chronic rheumatoid arthritis and obtained results identical with the ones described by those workers. On the supposition that the therapeutic effect of this method results from the alteration of desoxy-corticosterone acetate (DCA) into a cortisone-like substance through the redox action of the ascorbic acid, he used for the same purpose other sterones. The intramuscular injection of both testosterone (25 mg.) and progesterone (2 mg.) followed by one gram of ascorbic acid, injected intravenously, have produced the same therapeutic effect as the method of Lewin and Wassen. Total aqueous extract of adrenal cortex (cortine) and of estrone were less active; and dehydro-cholic acid proved completely ineffective. (Lancet, 21 Jan. '50, M. Landsberg)

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Desoxycorticosterone Acetate and Ascorbic Acid in Rheumatoid Arthritis: The preliminary communication of Lewin and Wassen on the treatment of rheu-matoid arthritis with desoxycorticosterone acetate and ascorbic acid prompted the author, working in St. Bartholomew's Hospital, London, to try this treat-ment on outpatients. The further correspondence which has varied in the opinions expressed stimulated him to write and mention the results he has had in treatment in 7 cases. All 7 patients, quite unselected as they appeared in the clinic, have shown improvement to a greater or lesser extent. He has been seeing them all regularly and no form of therapy has been of any avail until now. Of the 7 patients, one with an acute case which has been getting

steadily worse for the past 6 months, showed quite a dramatic improvement. Of the other 6 who were all chronic, one patient produced the startling results which Lewin and Wassen report. She had immediate symptomatic relief and now after 5 injections given in the course of 3 weeks is completely symptom-free and is walking better than she has done for 8 years. All her joints are symptomatically and clinically normal; before, she had considerable swelling and pain. Her last injection gave symptomatic relief for 7 days. The others have been slower in their response and have shown improvement only after from 3 to 5 injections given at short intervals. Of these, a woman of 63 is better than she has been for over a year. The improvement of the other 4 has been less dramatic but always quite definite, both symptomatically and clinically.

The fact that no improvement may be obtained after one, 2, 3, or even 4 injections should not discourage one from continuing, because, improvement may be slow in starting. (Letter to the Editor, Lancet, 21 Jan. '50, J. A. Robertson)

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Desoxycorticosterone Acetate and Ascorbic Acid in Rheumatoid Arthritis: In a letter to the editor of Lancet (21 Jan. '50), Faysal Nashat of Bagdad, Iraq, states that he has used the method reported by Lewin and Wassen in 4 cases of established rheumatoid arthritis and that the results were far from unsatisfactory. The patients were women aged 36, 42, 28, and 60, who had suffered from the disease for 8, 2, one, and one years respectively. They were more or less crippled and complaining of pain which at times was severe and for which they had tried without avail all analgesics, including morphine in one case.

They all responded within from 10 to 30 minutes to the combined administration of 5 mg. of desoxycorticosterone acetate and one Gm. of ascorbic acid injected intramuscularly. Pain was nullified in all cases, and mobility at least partly restored. In fact, one patient, bedridden for the last 18 months could walk unaided for the first time after the second injection. The relief lasted from 6 to 8 hours after the first injection and from 16 to 24 hours after the eighth injection (the last so far given). All the patients are enthusiastic and thankful, being able to perform most of their household work without pain.

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Tissue Studies in DDT Handlers: The object of this study was to determine the tissue level of DDT in handlers failing to exhibit clinical neurologic manifestations as a result of prolonged environmental contact with this insecticide during malaria, insect pest, and rodent control operations on established Marine Corps bases. The employment of specific insecticide crews over long periods of time presented excellent opportunities for the potential build-up of toxic tissue levels.

Because of the active participation of military personnel in preventive medicine programs on overseas bases and in the continental United States, a preliminary study was conducted by the investigators on a long series of laborers presenting unusual and prolonged environmental contact with DDT. A special effort was made to obtain the cooperation of those persons who presented histories of lengthy contact without regards to medical examination as the primary method of separation. Selected individuals most likely to demonstrate DDT concentrations in fat depots of the body were taken from experienced malaria, pest, and rodent control personnel. Their chief occupations consisted of compounding and mixing DDT-oil formulations, the dissemination of these solutions by means of the DDT-fog generator, the application of larvicides and adulticides by means of knapsack and power sprayers or the distribution of DDT dusts by hand-operated dusters in routine pest control operations.

The present study represents the first effort chemically to detect DDT in biopsied fat from apparently healthy human subjects. In addition to tissue examination, 24-hour urine samples, feces and whole and citrated blood were obtained for chemical analyses. In the first series recently completed, no DDT was detected in the material under study from 16 individuals detailing histories of exposure by contact for periods varying from 6 months to 3 years; one subject presented a history of daily contact for a period of 5 years.

These negative results obtained from human volunteers are considered to be important and significant. Because DDT is preferentially contained in fat, its presence represents actual storage rather than passive or temporary flooding of organs of fatty tissues. The authors are led to conclude, therefore, that, (a) handlers utilizing normal precautionary measures not only fail to exhibit symptoms of DDT poisoning, but, (b) show no chemically detectable accumulation of DDT in body fat as a result of prolonged external contact with this agent. It likewise indicates that malaria control operators can safely utilize the services of personnel over long periods of time without fear of developing toxic tissue levels of DDT.

Military personnel and their dependents exposed to DDT in areas where nightly fog applications are made have not exhibited any untoward reactions to oil fog or DDT proper. In many instances these subjects have been residents of endemic fog areas for 3 years or longer. It is felt that the cross-section of population represented on 3 large Marine Corps bases provided an adequate sample from which the epidemiologic and clinical observations were made.

Adequate personnel protection, adherence to recommendations for use, and the careful indoctrination and rotation of exposed individuals through varied duties within the organization have been in part responsible for the small number of toxicities known to date. (Proj. NM 005 052/7, Rep. No. 1, 2 Dec. '49, Nav. Med. Field Res. Lab., Camp Lejeune, N. C., W. J. Perry and L. J. Bodenlos)

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Course in Medical Aspects of Special Weapons and Radioactive Isotopes: The U. S. Naval Medical School, Bethesda, Maryland, announces another course of instruction for Reserve medical and dental officers in Medical Aspects of Special Weapons and Radioactive Isotopes. It will commence Monday, 22 May 1950 and continue through 26 May 1950. (This course is in addition to the one to be held at the Naval Medical School from 27 to 31 March 1950.)

One of the purposes of this course is to provide Reserve medical and dental officers with information, technics, and problems likely to be confronted in the field of radioactivity. This course is similar to those formerly conducted at the U. S. Naval Medical School.

This course is conducted primarily for the benefit of inactive Reserve medical and dental officers; however, a limited number of medical and dental officers of the regular Navy and Reserve officers on active duty in the Washington area may attend providing arrangements can be made by the individuals with their local commanding officers and the Commanding Officer of the U. S. Naval Medical School, Bethesda, Maryland.

Inactive Reserve medical and dental officers who desire to attend this course should submit a request for training duty to the commandant of their local naval district. All requests should reach the commandant's office at the earliest practicable date. The facilities available at the Naval Medical School make it necessary to restrict attendance to 200 Reserve medical and dental officers.

Meals and a limited number of sleeping quarters will be available for those officers who desire such accommodations. (Reserve Div., BuMed)

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Training Course for Dental Corps Reserves: A 2 weeks' training course for approximately 44 Volunteer Naval Reserve dental officers will be conducted at the Naval Dental School, National Naval Medical Center, Bethesda, Maryland, from 12 to 25 April 1950. This training duty will consist of professional and military subjects appropriate to dental officers and will be similar to the courses conducted at the Naval Dental School during the past 2 years.

Volunteer Reserve dental officers desiring to attend this course should submit requests to their district commandant. (Dental Div., BuMed)

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Joint Letter

Departments of the Army, the Navy, and the Air Force

BUMED CIRCULAR LETTER 50-14

Subj: Yellow Fever Immunization Requirements - Pakistan

This letter soon to be released and published in the Navy Department Bulletin (probably 28 February 1950 issue), states (1) that in the case of travelers from or via certain areas, immunization against yellow fever must be accomplished not less than 15 days nor more than 4 years before arrival, (2) that the only currently acceptable certificate is the International Certificate of Inoculation and Vaccination, Public Health Service Form 731 (IHR), authenticated with the seal of the Public Health Service and showing the origin and batch number of the vaccine, the date of inoculation, the signature, position title and location of the inoculating officer, and the signature and address of the holder, (3) that the vaccine manufactured at Hamilton, Montana by the National Institutes of Health, USPHS, is accepted as approved by all nations, and (4) gives information concerning the various locations at which the certificates may be obtained and the seal affixed.

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BUMED CIRCULAR LETTER 50-15 JointLtr 3 February 1950

From: Chief of Naval Personnel
Chief of Bureau of Medicine and Surgery
Commandant of the Marine Corps

To: Commanding Officers, Naval Hospitals, CLUSA
Commanders of All Naval Training Centers
Commanding Officers of all MarCorps Activities, CLUSA

Subj: Personnel, Enlisted and Inducted; Medical Reports Pertaining to Disposition of, When on the Sick List

Refs:
(a) BuPers-BuMed-MarCorps Jt Ltr dtd 22 Nov 1948 (BuMed C/L 48-128), as modified by BuPers-BuMed-MarCorps Jt Ltr dtd 1 June 1949 (BuMed C/L 49-64)
(b) SecNav dispatch 282223 dtd Sept 1949
(c) BuMed ltr File P3-5/P19-1 dtd 28 Sept 1949
(d) Regulations prescribed by SecNav for the administration of Title IV of the Career Compensation Act of 1949
(e) Instructions prescribed by SecNav for the administration of Title IV of the Career Compensation Act of 1949

1. References (a), (b) and (c) are hereby cancelled.

2. Reference (d) establishes Clinical Boards and assigns to such Boards the duty of reporting upon the state of health of members of the Service who are obviously incapacitated for the performance of duty or in whose cases there may be reasonable doubt as to fitness to perform duty when such unfitness results from physical disability. It provides that individual cases shall be referred to a Clinical Board in such manner as the Convening Authority directs and that requests for such referral may be made to such authority when it is necessary to determine the physical fitness of an individual in the Naval Service. The determination of physical fitness in this manner is indicated when discharge, separation or retirement of physically disabled personnel is under consideration. In the event a clinical report is required in such cases because physical disability renders the member unfit for service and court martial proceedings or investigative proceedings which might lead to court martial are pending, indicated, or have been completed, or in cases of uncompleted sentences of courts martial involving confinement, such reports shall be submitted to the Bureau of Naval Personnel or Headquarters, Marine Corps, as appropriate, via the Bureau of Medicine and Surgery, for further disposition in accordance with the provisions of paragraph 9, Part I of reference (e). It is emphasized that the collection of the pertinent facts relating to the disciplinary features of a case is not a function of the Clinical Board, but shall be accomplished by the Convening Authority.

3. Except for the above, Boards of Medical Survey may continue to perform previously assigned functions. Such Boards shall submit reports on those personnel on the sick list in accordance with the following provisions:

a. Disciplinary:

When court martial proceedings or investigative proceedings which might lead to court martial are pending, indicated, or have been completed, and in cases of uncompleted sentences of courts martial involving confinement and the disciplinary features of the case warrant resolution prior to or in connection with further disposition (excepting that where the primary consideration is discharge, separation or retirement of the case because of unfitness resulting from physical disability the report is to be made by a Clinical Board).

b. Those who are unfit for service by reason of one of the following conditions:

Addiction (drug)	Maladjustment, situational, acute
Aggressive reaction	Mental deficiency, primary
Alcoholism	Motion sickness
Anti-social personality	Paranoid Personality
Asocial (amoral) personality	Passive aggressive reaction
Cyclothymic personality	Passive dependency reaction
Emotional instability reaction	Primary childhood behavior reaction
Inadequate personality	Schizoid personality
Immaturity with symptomatic habit reaction	Specific learning defect
	Sexual deviate

It should be noted that the above diagnoses represent inherent pre-existing defects which warrant discharge for administrative reasons when they impair functional usefulness to such extent as to constitute military unfitness. Such conditions are to be distinguished from those which cause physical disability and thereby incapacitate the individual so as to warrant retirement or separation by reason of physical disability. It is emphasized that when these defects are primary as an inherent part of the personality structure, and not secondary to disease or injury, they are to be reported upon by Boards of Medical Survey; whereas when the secondary effect of disease or injury they are to be reported upon by Clinical Boards.

c. Those whose return to full duty may be facilitated by serving a period up to six months in a limited duty status.

d. Boards of Medical Survey shall report upon an individual on completion of treatment and when considered ready for duty provided such a formal report is deemed appropriate.

e. Boards of Medical Survey shall report upon an individual after each successive period of six-months hospitalization when retention for further treatment is indicated.

4. Addressees are hereby authorized to take final action on certain Reports of Medical Survey in the case of subject personnel, as follows:

a. When the Board of Medical Survey recommends return to duty;

b. When the Board of Medical Survey recommends retention for further treatment;

c. When (subject to restrictions listed in paragraph 5 below) the Board of Medical Survey recommends discharge of an individual having one of the diagnoses listed in sub-paragraph 3(b) above, and all the following conditions are met;

(1) The individual concerned does not have a diagnosis of Addiction (drug), Alcoholism, Asocial (Amoral) Personality, or Sexual Deviate;

(2) The individual concerned has less than eight (8) years' active service;

(3) The individual concerned indicates in writing that he has been informed of the findings and does not desire to submit a statement in rebuttal.

5. In connection with the provisions of subparagraph 4(c) above, the following restrictions apply:

a. Commanders, All Naval Training Centers are authorized to effect such discharges only in the cases of Naval Personnel (USN, USNEV, USNR, and inducted), when discharge from Service is recommended.

b. Commanding Officers, U. S. Naval Hospitals, CLUSA, are authorized to effect such discharges only in the cases of Naval Personnel (USN, USNEV, USNR, and inducted), when discharge from Service is recommended.

c. Commanding Officers, All Marine Corps activities, CLUSA, are authorized to effect such discharge only in the cases of Marine Corps personnel (USMC, USMC-V, USMCR, and inducted), when discharge from Service is recommended.

d. Discharges effected under this authority shall be by reason of "Convenience of the Government," rather than by reason of Unsuitability, Unfitness, or Misconduct, and in all cases on the reverse side of discharge certificates, abreast the entry "Authority," references shall be entered as follows: For Naval personnel, article C-10305 (f), BuPers Manual 1948, and this joint letter; for Marine Corps personnel, paragraph 10271, MCM 1949, and this joint letter. In cases where the Commanding Officer feels that discharge should not be for the "Convenience of the Government," but for Unsuitability, Unfitness, or Misconduct, or for any other reason, they shall be referred to BuPers or MarCorps as appropriate, via BuMed for final decision. Cases in this category would be those where the record of the individual concerned shows (1) commission of serious military offenses, (2) a generally unsatisfactory conduct record, (3) for other good and sufficient cause in the opinion of the Commanding Officer. In submitting recommendations for discharge by reason of Unsuitability, Unfitness, Misconduct, or for any other reason, the procedures prescribed by applicable articles in BuPers and MarCorps Manuals shall be followed.

6. In the cases of Navy personnel (USN, USNEV, USNR, and inducted), when final action is taken by addressees on Reports of Medical Survey in accordance with paragraphs 4 and 5(a) or 5(b) of this letter, the original and one copy of the report shall be forwarded to BuPers via BuMed indicating by endorsement thereon the action taken.

7. In the cases of Marine Corps personnel (USMC, USMC-V, USMCR, and inducted), when the Commanding Officer of a Naval Hospital has approved a Report of Medical Survey and he is authorized to take final action locally under the provisions of paragraph 4(a) and (b) above, he

shall forward the original and one copy of the report to the Commandant of the Marine Corps via BuMed indicating by endorsement thereon the action taken. If discharge from Service is recommended and final action can be taken locally only by the Commanding Officer of the local Marine Corps activity (see paragraph 5(c)), the Commanding Officer of the Naval Hospital shall forward the original and four legible copies to the Commanding Officer of the Marine Corps actively concerned. Upon receipt of such approved reports and when the Commanding Officer of the Marine Corps activity has taken final action, the original and one copy of the report shall be forwarded to the Commandant of the Marine Corps, via BuMed and one copy returned to the Commanding Officer of the Naval Hospital from which received showing by endorsement thereon the action taken.

a. Those involving personnel recommended for return to limited duty in accordance with paragraph 3(c) above.

b. Those involving personnel when court martial proceedings or investigative proceedings which might lead to court martial are pending, indicated, or have been completed, and in cases of uncompleted sentences of courts martial involving confinement.

c. Those in which the individual submits a statement in rebuttal.

d. Those wherein discharge is recommended, and the individual concerned has completed eight (8) or more years' active service.

e. Those in which the addressee having the authority to take final action considers that the individual should be discharged by reason other than Convenience of the Government.

f. Those in which the addressee having authority to take final action considers it preferable to forward the report to the Navy Department for action.

g. Those diagnosed Sexual deviate, Addiction (drug), Alcoholism, or Asocial (amoral) Personality.

9. a. When the Commanding Officer of a Naval Hospital submits a Report of Medical Survey to BuPers or MarCorps via BuMed for final action, in the case of an enlisted or inducted person, he may whenever he considers that the individual does not require retention in the Hospital, release him from the sick list and transfer him in a duty status to an appropriate duty station to await Navy Department action.

b. U. S. Navy personnel released from the sick list under the above conditions, if recommended for discharge, should be transferred from the hospital to a Naval activity nearest their home of record that is authorized to effect discharge, or, if recommended for return to duty, to a Receiving Station or other appropriate naval command nearest the hospital. U. S. Marine Corps personnel should be transferred to the Marine Corps Barracks nearest the hospital.

c. In the above cases, the Commanding Officer of the Naval Hospital shall indicate, by endorsement on the Report of Medical Survey, the temporary disposition so effected. The Report shall be submitted to BuPers or MarCorps, as appropriate, via BuMed in original and four copies. If the man is transferred, one additional copy shall be forwarded to the new duty station.

d. At the discretion of the Commanding Officer of the Receiving Station or Marine Barracks and with the advice of the Medical Officer of the Station in each individual case, these men may be assigned such specific duties as are compatible with and will not aggravate their physical condition, while awaiting action by the Chief of Naval Personnel or Commandant of the Marine Corps, as appropriate.

10. a. When an enlisted or inducted person who is a patient in a naval hospital is ordered to appear before a Physical Evaluation Board, the Commanding Officer of the Naval Hospital may, when he considers that the individual does not require retention in the hospital, release him from the sick list and transfer him to an appropriate duty station to await action in the case.

b. U. S. Navy personnel released from the sick list under the above condition should be transferred to a naval activity near the naval establishment in which the Physical Evaluation Board before which the individual is to appear is convened and U. S. Marine Corps personnel should be transferred to the Marine Corps Barracks near such naval establishment.

c. In the above cases the Commanding Officer of the naval hospital shall indicate, on copies of the orders in the case, the temporary disposition so effected and cite this letter as authority. One copy of the orders bearing the indicated disposition shall be forwarded to each, BuMed, BuPers or MarCorps as appropriate, and the Commanding Officer of the station of transfer.

d. At the discretion of the Commanding Officer of the station of transfer and with the advice of the Medical Officer of the station in each individual case, these men may be assigned such specific duties as are compatible with and will not aggravate their physical condition, while awaiting action by the Secretary of the Navy.

--BuPers. J. W. Roper --BuMed. C. A. Swanson --MarCorps. C. B. Cates

Approved: 3 Feb 1950, Francis P. Matthews, Secretary of the Navy

NOTE: This joint letter appears in the 15 February Navy Department Bulletin as an enclosure to an All Ships and Stations letter issued by the Secretary of the Navy.

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BUMED CIRCULAR LETTER 50-16 7 February 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Publications; Downgrading of

Ref: (a) BuMed CirLtr No. 49-144; Navy Department Bulletin of 15 Nov 1949, 49-808

1. Reference (a) downgraded several publications from restricted to unclassified.

2. Paragraph 1(b) of reference (a), which reads "NavMed 630 - Epidemiology of Diseases of Naval Importance in Micronesia 1944 RESTRICTED," should be corrected to read, "NavMed 630 - Epidemiology of Diseases of Naval Importance in China 1944 RESTRICTED." C. A. Swanson

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BUMED CIRCULAR LETTER 50-17 9 February 1950

From: Chief, Bureau of Medicine and Surgery
To: Commandants, All Naval Districts (less 10, 15, and 17) and Commandant, Potomac River Naval Command

Subj: Dental Commissioning Allowance List for Naval Reserve Armories and Reserve Dental Officers Performing "Appropriate Duty"

Ref: (a) BuPers ltr Pers-1D9-be, Serial F:743 of 29 Apr 1949
(b) BuMed CirLtr No. 47-100
(c) BuMed CirLtr No. 49-86

Encl: (1) Dental Commissioning Allowance List for Naval Reserve Armories

This letter supersedes references (b) and (c) and states (1) that procurement of the allowance of dental material listed in enclosure (1) is authorized, at the discretion of addressees, when required at Naval Reserve Armories, or at Naval Reserve Training Centers for use by dental officers ordered to perform "appropriate duty," and (2) that material shall be requisitioned from the nearest naval medical supply depot on NAVMED Form 4, screened or prepared by addressees as applicable.

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BUMED CIRCULAR LETTER 50-18 10 February 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations (Advance copies to CO's, NavHosps)

Subj: Reporting of Air Force Personnel Treated in Naval Medical Facilities

Ref: (a) BUMED CirLtr No. 49-154 of 18 Nov 1949

1. With the increase in joint hospitalization among the various armed services, it has become increasingly important that complete and accurate reports be submitted for all military personnel treated in naval medical facilities. Enclosure (1) to reference (a) directs that NAVMED-F (Individual Statistical Report of Patient) for Army and Air Force patients be forwarded to the cognizant Surgeon General.

2. It is further directed that in the case of Air Force patients any W.D.A.G.O. forms 8-24 received with such patients be forwarded with NAVMED-F to the Surgeon General, U. S. Air Force, Washington 25, D. C. upon the completion of treatment. When Air Force patients are transferred to other military medical facilities before the completion of treatment, both NAVMED-F and any W.D.A.G.O. forms 8-24 shall accompany the patient.

3. In the event of the death of an Air Force patient within a naval activity, in addition to the forms mentioned above, a copy of NAVMED-N (Certificate of Death) shall be forwarded to the Surgeon General of the Air Force.

4. Nothing in this letter shall be construed as changing existing procedures in the case of Army patients in naval facilities. C. A. Swanson

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

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